

Application No. 09/543,679  
Supplemental Amendment dated June 14, 2004  
Reply to Office Action of February 11, 2004

**Amendments to the Claims:**

**In the Claims:**

Please amend the claims as follows:

1-91. (Cancelled)

92. (Currently amended) An in vivo method of delivering a pharmaceutical composition to a target polynucleotide comprising administering to the airways of a subject said pharmaceutical composition of a respirable or inhalable particle size of 0.5 um to 10 um in size or 10 um to 500 um in size comprising at least one antisense oligonucleotide to said target polynucleotide effective to alleviate hyper-responsiveness to adenosine or increased levels of adenosine, or to alleviate bronchoconstriction, asthma, or lung allergy, wherein the oligonucleotide is 7 to 60 nucleotides long and up to and including about 15% or less adenosine, and the oligonucleotide is antisense to the initiation codon, the coding region of the 5' and 3' intron-exon junctions of a gene encoding a protein associated with hyper-responsiveness, to and/or increased levels of, adenosine, bronchoconstriction, asthma and/or lung allergy(ies) and/or inflammation, or being antisense to the corresponding mRNA thereof, the nucleic acid comprising one or more oligonucleotide(s), pharmaceutically or veterinarily acceptable salts of the oligonucleotide(s), mixtures of the oligonucleotide(s) or their salts.

93. (Previously Presented) The method of claim 92, wherein the antisense oligonucleotide comprises 10% or less adenosine.

94. (Previously Presented) The method of claim 93, wherein the antisense oligonucleotide comprises 5% or less adenosine.

95. (Previously Presented) The method of claim 94, wherein the antisense oligonucleotide comprises 2% or less adenosine.

96. (Previously Presented) The method of claim 95, wherein the antisense oligonucleotide is adenosine-free.

97. (Previously Presented) The method of claim 92, wherein the antisense oligonucleotide is 10 to 36 nucleotides long.

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98. (Previously Presented) The method of claim 97, wherein the antisense oligonucleotide is 12 or 21 nucleotides long.

99. (Previously Presented) The method of claim 92, wherein the pharmaceutical composition is administered by inhalation directly to the lung of the subject.

100. (Previously presented) The method of claim 92, wherein the antisense oligonucleotide is antisense to the initiation codon, the coding region or the 5' or 3' intron-exon junction of a nucleic acid encoding a target polypeptide associated with pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome, cystic fibrosis, allergic rhinitis, pulmonary hypertension, emphysema, chronic obstructive pulmonary disease, bronchitis, and lung cancer, or is antisense to the corresponding mRNA thereof.

101. (Previously presented) The method of claim 92, wherein the particle size is 0.5  $\mu\text{m}$  to 10  $\mu\text{m}$  in size.

102. (Previously presented) The method of claim 101, wherein the particle size is 10  $\mu\text{m}$  to 500  $\mu\text{m}$  in size.

103. (Previously presented) The method of claim 92, wherein the pharmaceutical composition further comprises a surfactant.

104. (Previously presented) The method of claim 92, wherein the hyper-responsiveness to adenosine, hyper-responsiveness to increased levels of adenosine, hyper-responsiveness to increased levels of an adenosine receptor, bronchoconstriction, asthma, lung allergy, or lung inflammation is associated with pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome, cystic fibrosis, allergic rhinitis, pulmonary hypertension, emphysema, chronic obstructive pulmonary disease, bronchitis, and lung cancer.

105. (Previously presented) The method of claim 92, wherein the antisense oligonucleotide is administered in an amount of about 0.01 to about 150 mg/kg body weight.

106. (Previously presented) The method of claim 92, wherein said method is a prophylactic or therapeutic method.

107. (Previously presented) The method of claim 92, wherein the antisense oligonucleotide is antisense to the initiation codon, the coding region or the 5' or 3' intron-exon junctions of a gene encoding bradykinin B2 receptor.

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108. (Previously presented) The method of claim 92, wherein the antisense oligonucleotide comprises at least one mononucleotide is linked or modified by one or more of phosphorothioate, phosphorodithioate, methylphosphonate, phosphoramidate, boranophosphate, 3' - thioformacetal, triformacetal, carbamate, phosphotriester, formacetal, 2'-O-methyl, thioformacetal, 5'-thioether, carbonate, 5'-N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene (methylimino), methyleneoxy (methylimino), methoxyethyl, C<sub>3</sub>-substituted nucleotide and methyloxyethyl.

109. (Previously presented) A pharmaceutical composition comprising at least one antisense oligonucleotide that is antisense to a target polynucleotide and when delivered to the airways of a subject is effective to alleviate hyper-responsiveness to adenosine or increased levels of adenosine, or to alleviate bronchoconstriction, asthma, or lung allergy, wherein the oligonucleotide is 7 to 60 nucleotides long and up to and including about 15% or less adenosine, wherein the oligonucleotide is antisense to an initiation codon, a coding region or a 5' or 3' intron-exon junctions of a gene encoding an adenosine A1, A2a, A2b or A3 receptor or anti-sense to their respective mRNA thereof, wherein said pharmaceutical composition is of a respirable or inhalable particle size of 0.5  $\mu\text{m}$  to 10  $\mu\text{m}$  in size or 10  $\mu\text{m}$  to 500  $\mu\text{m}$  in size and comprises pharmaceutically and veterinarily acceptable salts of the oligo(s) or mixtures thereof and comprises a surfactant that may be operatively linked to the nucleic acid.

110. (Previously presented) The pharmaceutical composition of claim 109, wherein the antisense oligonucleotide comprises 10% or less adenosine.

111. (Previously presented) The pharmaceutical composition of claim 110, wherein the antisense oligonucleotide comprises 5% or less adenosine.

112. (Previously presented) The pharmaceutical composition of claim 111, wherein the antisense oligonucleotide comprises 2% or less adenosine.

113. (Previously presented) The pharmaceutical composition of claim 112, wherein the antisense oligonucleotide is adenosine-free.

114. (Previously presented) The pharmaceutical composition of claim 109, wherein the antisense oligonucleotide is 10 to 36 nucleotides long.

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115. (Previously presented) The pharmaceutical composition of claim 114, wherein the antisense oligonucleotide is 12 or 21 nucleotides long.

116. (Previously presented) The pharmaceutical composition of claim 109, wherein the pharmaceutical composition is delivered by inhalation directly to the airway or lung of the subject.

117. (Previously presented) The pharmaceutical composition of claim 109, wherein the antisense oligonucleotide is antisense to the initiation codon, the coding region or the 5' or 3' intron-exon junction of a nucleic acid encoding a target polypeptide associated with pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome, cystic fibrosis, allergic rhinitis, pulmonary hypertension, emphysema, chronic obstructive pulmonary disease, bronchitis, and lung cancer, or is antisense to the corresponding mRNA thereof.

118. (Previously presented) The pharmaceutical composition of claim 109, wherein the particle size is 0.5  $\mu\text{m}$  to 10  $\mu\text{m}$  in size.

119. (Previously presented) The pharmaceutical composition of claim 109, wherein the particle size is 10  $\mu\text{m}$  to 500  $\mu\text{m}$  in size.

120. (Previously presented) The pharmaceutical composition of claim 109, wherein the pharmaceutical composition further comprises a surfactant.

121. (Previously presented) The pharmaceutical composition of claim 109, wherein the hyper-responsiveness to adenosine, hyper-responsiveness to increased levels of adenosine, hyper-responsiveness to increased levels of an adenosine receptor, bronchoconstriction, asthma, lung allergy, or lung inflammation is associated with pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome, cystic fibrosis, allergic rhinitis, pulmonary hypertension, emphysema, chronic obstructive pulmonary disease, bronchitis, and lung cancer.

122. (Previously presented) The pharmaceutical composition of claim 109, wherein the antisense oligonucleotide is delivered in an amount of about 0.01 to about 150 mg/kg body weight.

123. (Previously presented) The pharmaceutical composition of claim 109, wherein the delivery of said pharmaceutical composition is prophylactic or therapeutic.

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124. (Previously presented) The pharmaceutical composition of claim 109, wherein the antisense oligonucleotide is antisense to the initiation codon, the coding region or the 5' or 3' intron exon junctions of a nucleic acid encoding bradykinin B2 receptor.

125. (Previously presented) The pharmaceutical composition of claim 109, wherein the antisense oligonucleotide comprises at least one mononucleotide is linked or modified by one or more of phosphorothioate, phosphorodithioate, methylphosphonate, phosphoramidate, boranophosphate, 3'-thioformacetal, triformacetal, carbamate, phosphotriester, formacetal, 2'-O-methyl, thioformacetal, 5'-thioether, carbonate, 5'-N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene (methylinino), methyleneoxy (methylinino), methoxyethyl, C<sub>5</sub>-substituted nucleotide and methoxyethyl.